

Mutations in Retroviral Genes Associated with Drug Resistance

John W. Mellors¹, Raymond F. Schinazi², and Brendan A. Larder³

¹ University of Pittsburgh Medical Center, Montefiore University Hospital, Infectious Diseases Division, 200 Lothrop Street, Pittsburgh, PA 15213-2582.

² Emory University/VAMC, 1670 Clairmont Rd., Decatur, GA 30033.

³ Glaxo Wellcome Medicines Research Centre, Gunnels Wood Rd., Stevenage, Herts, SG1 2NY, UK.

Introduction

The emergence of drug-resistant variants of HIV continues to be of prime interest in the fields of HIV disease pathogenesis and antiretroviral chemotherapy. Drug resistance is the inevitable consequence of incomplete suppression of HIV replication. The rapid replication rate of HIV and its inherent genetic variation lead to the generation of a seemingly limitless number of viral variants that exhibit drug resistance. The growing number of drug resistance mutations listed in these revised tables stands as a testimony to the genetic flexibility of HIV. When the first resistance table was published in 1994 (*International Antiviral News* 2(5):72-75) only 42 different mutations were listed. This new update lists 143 mutations, a 240 per cent increase over a 2-year period. The revised tables include, for the first time, sections on HIV binding/fusion inhibitor resistance, and multidrug resistance. Although the tables are quite comprehensive, the reader should be reminded that the mutations described are predominately found in clade B virus and not in other HIV genotypes.

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Mutations in HIV-1 RT that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
M 41 L	ATG to TTG/CTG	Nucleoside RTI	AZT	?	Y	4		M41L/T215Y: 60-70-fold; M41L/D67N/ K70R/T215Y: 180-fold.	(1,2,3)
K 65 R	AAA to AGA	Nucleoside RTI	1592U89	Y	N	3		K65R/L74V and/or Y115F with M184V: 10 fold; K65R/M184V: 8-fold	(4,5)
K 65 R	AAA to AGA	Nucleoside RTI	ddC	Y	Y	4-10			(6,7)
K 65 R	AAA to AGA	Nucleoside RTI	ddI	Y	Y	4-10	ddI; ddC; PMEA; 3TC	Infrequently observed in patients receiving ddI or ddC	(6,7)
K 65 R	AAA to AGA	Nucleoside RTI	DXG	Y	?	8	other dioxolane derivatives	K65R reverses AZT resistance in D67N/K70R/T215Y/K219Q background	(8,9)
K 65 R	AAA to AGA	Nucleoside RTI	PMEA	Y	?	10-25			(10,11)
D 67 N	GAC to AAC	Nucleoside RTI	AZT	Y	Y			D67N/K70R/T215Y/K219Q: 120-fold; M41L/D67N/K70R/T215Y: 180-fold.	(1,2,3)
T 69 D	ACT to GAT	Nucleoside RTI	ddC	N	Y	5			(12)
K 70 E	AAA to GAA	Nucleoside RTI	PMEA	Y	?	9	3TC; PFA: 2-fold hypersusceptibility		(13)
K 70 R	AAA to AGA	Nucleoside RTI	AZT	Y	Y			D67N/K70R/T215Y/K219Q: 120-fold	(1,2,3)
L 74 I	TTA to ATA	HIV-1 Specific RTI	HBY 097	Y	?				
L 74 V	TTA to GTA	HIV-1 Specific RTI	HBY 097	Y	?				
L 74 V	TTA to GTA	Nucleoside RTI	1592U89	Y	N	4		K65R/L74V and/or Y115F with M184V: 10 fold; L74V/M184V: 9-fold resistance; L74V/Y115F/M184V: 11-fold	(4,5)
L 74 V	TTA to GTA	Nucleoside RTI	ddI	N	Y	5-10	ddC	Can reverse effect of T215Y AZT resistance mutation	(14)
L 74 V	TTA to GTA	Nucleoside RTI	DXG	Y	?	4			(9)
V 75 I	GTA to TTA	HIV-1 Specific RTI	HBY 097	Y	?			Compensates for negative effect of the G190E mutation on RT activity	(15)
V 75 L	GTA to ATA	HIV-1 Specific RTI	HBY 097	Y	?				

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Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
V 75 T	GTA to ACA	Nucleoside RTI	d4T	Y	Y	7	ddI; ddC; d4C; (-)-FTC	Observed with d4T selection in vitro, and rarely in patients receiving d4T	(16,17)
W 88 G	TGG to GGG	Pyrophosphate Analogue RTI	Foscarnet (PFA)	Y	Y	5	Hypersusceptibility to AZT	Observed after selection with AZT and PFA; suppresses effects of AZT mutations while maintaining 3.5- to 4.7-fold PFA resistance	(18,19)
W 88 S	TGG to TCG	Pyrophosphate Analogue RTI	Foscarnet (PFA)	N	Y	2-4	Wild-type susceptibility to AZT	Partially suppresses effects of AZT mutations, but resistance to PFA is lost	(18,20)
E 89 G	GAA to GGA	Pyrophosphate Analogue RTI	Foscarnet (PFA)	Y	N	14		Isolated by screening RT clones for ddGTP resistance	(21)
E 89 K	GAA to GGA	Pyrophosphate Analogue RTI	Foscarnet (PFA)	Y	N	> 16		Suppresses effects of AZT resistance mutations	(19)
L 92 I	TTA to ATA	Pyrophosphate Analogue RTI	Foscarnet (PFA)	Y	N	8		Suppresses effects of AZT resistance mutations	(19)
A 98 G	GCA to GGA	HIV-1 Specific RTI	L-697,661	N	Y	8			(22)
A 98 G	GCA to GGA	HIV-1 Specific RTI	Nevirapine	N	Y				(23)
L 100 I	TTA to ATA	HIV-1 Specific RTI	BHAP U-88204E	Y	?				(24,25)
L 100 I	TTA to ATA	HIV-1 Specific RTI	DMP 266 (L-743,726)	Y	?	8-11		Combinations of mutations needed for high-level resistance; L100I/V108I: 1,000-fold; L100I/V179D/Y181C: 1,000-fold	(26,27,28)
L 100 I	TTA to ATA	HIV-1 Specific RTI	L-697,661	Y	N	2			(22)
L 100 I	TTA to ATA	HIV-1 Specific RTI	Nevirapine	N	Y				(29)
L 100 I	TTA to ATA	HIV-1 Specific RTI	TIBO R82150	Y	?	> 100		Can reverse effects of AZT resistance mutations	(30,31,32)

Mutations in HIV-1 RT that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold- resistance	Cross-resistance (-fold)	Comments	Refs
L 100 I	TTA to ATA	HIV-1 Specific RTI	TIBO R82913	Y	?			Found in combination with E138K	(31,33)
L 100 I	TTA to ATA	HIV-1 Specific RTI	UC-68 (638532)	Y	?	70			(34)
L 100 I	TTA to ATA	HIV-1 Specific RTI	UC-70 (638534)	Y	?	758			(35)
L 100 I	TTA to ATA	HIV-1 Specific RTI	UC-781	Y	?	20		Activity of UC-781 versus L100I, K103N, V106A, E138K, Y181C and Y188L reduced by 2-, 7-, 1.5-, 1.5-, 5- and 150-fold, respectively, compared to wild type	(36,37)
L 100 I	TTA to ATA	HIV-1 Specific RTI	UC-84 (615985)	Y	?	> 40, > 33			(35,38)
K 101 E	AAA to GAA	HIV-1 Specific RTI	8-Chloro-TIBO R091767	?	Y				(39)
K 101 E	AAA to GAA	HIV-1 Specific RTI	BHAP U-87201E (ateviridine)	N	Y			K101E, Y188H, E233Y and K238T observed with U-87201E/AZT combination therapy	(40,41)
K 101 E	AAA to GAA	HIV-1 Specific RTI	DMP 266 (L-743,726)	Y	?	1,000			(26,27)
K 101 E	AAA to GAA	HIV-1 Specific RTI	L-697,661	N	Y	8			(22)
K 101 E	AAA to GAA	HIV-1 Specific RTI	UC-10 (645129)	Y	?			K101E/Y181C: 200-fold	(35)
K 101 E	AAA to GAA	HIV-1 Specific RTI	UC-38 (629243)	Y	?			K101E/G190E: > 100-fold; cross resistance to: TSAO-m ³ T, Nevirapine, TIBO R82913, BHAP U88204; susceptible to L697,661	(34,42)
K 101 E	AAA to GAA	HIV-1 Specific RTI	UC-57 (647014)	Y	?			K101E/Y181C: 58-fold	(35)
K 101 I	AAA to ATA	HIV-1 Specific RTI	UC-16	Y	?	10		K101I/G141E: 10-fold	(34)
K 101 Q	AAA to CAA	HIV-1 Specific RTI	Trovirdine	Y	?			Found in combination with V108I	(43,44)
K 103 N	AAA to AAC	HIV-1 Specific RTI	8-Chloro-TIBO R091767	?	Y				(39)
K 103 N	AAA to AAC	HIV-1 Specific RTI	BHAP U-87201E (ateviridine)	N	Y			K103N and Y181C observed with monotherapy	(40)

Mutations in HIV-1 RT that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
K 103 N	AAA to AAC	HIV-1 Specific RTI	BHAP U-90152 (delavirdine)	?	Y			K103N/Y181C seen with monotherapy and combination therapy	(45)
K 103 N	AAA to AAC	HIV-1 Specific RTI	DMP 266 (L-743,726)	Y	?	67			
K 103 N	AAA to AAC	HIV-1 Specific RTI	L-697,593	Y	?	20		K103N/Y181C: > 1,000-fold	(46)
K 103 N	AAA to AAC	HIV-1 Specific RTI	L-697,661	Y	Y	8		K103N and Y181C most common with monotherapy	(22,47)
K 103 N	AAA to AAC	HIV-1 Specific RTI	Loviride (R89439, α -APA)	Y	Y				(48)
K 103 N	AAA to AAC	HIV-1 Specific RTI	MKC-442 (I-EBU)	Y	?				(49)
K 103 N	AAA to AAC	HIV-1 Specific RTI	Nevirapine	N	Y				(29)
K 103 N	AAA to AAC	HIV-1 Specific RTI	TIBO R82913	Y	?	> 100		K103N/Y181C: > 1,000-fold	(24)
K 103 N	AAA to AAC	HIV-1 Specific RTI	UC-10 (645129)	Y	?	5			(34)
K 103 N	AAA to AAC	HIV-1 Specific RTI	UC-81 (615727)	Y	?	40			
K 103 Q	AAA to CAA	HIV-1 Specific RTI	L-697,661	N	Y	8			(47)
K 103 R	AAA to AGA	HIV-1 Specific RTI	Trovirdine	Y	?		Nevirapine; 9-chloro-TIBO	K103R/V179D: 500-fold; Found in combination with V179D or Y181C	(43,44)
K 103 T	AAA to ACA	HIV-1 Specific RTI	BHAP U-90152 (delavirdine)	?	Y				(45)
K 103 T	AAA to ACA	HIV-1 Specific RTI	UC-42	Y	N	100			(34)
V 106 A	GTA to GCA	HIV-1 Specific RTI	BHAP U-88204E	Y	?				(25)
V 106 A	GTA to GCA	HIV-1 Specific RTI	E-EBU-dM	Y	?				(50)
V 106 A	GTA to GCA	HIV-1 Specific RTI	Nevirapine	Y	Y	100		No effect on AZT resistance	(23,24,29,33)
V 106 A	GTA to GCA	HIV-1 Specific RTI	TIBO R82913	Y	?	100		No effect on AZT resistance	(33)
V 106 A	GTA to GCA	HIV-1 Specific RTI	UC-69 (646989)	Y	?			V106A/V181C: 166-fold	(35)

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Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
V 106 A	GTA to GCA	HIV-1 Specific RTI	UC-82	Y	?	13		Activity of UC-82 versus L100I, K103N, V106A, E138K, Y181C and Y188L reduced by 2-, 6-, 1.5-, 2-, 4- and 200-fold, respectively, compared to wild type	(36,37)
V 106 I	GTA to ATA	HIV-1 Specific RTI	HBY 097					Appears under lowered drug concentration selection	(51)
V 108 I	GTA to ATA	HIV-1 Specific RTI	DMP 266 (L-743,726)	Y	?			L100I/V108I: 1,000-fold	(26,27)
V 108 I	GTA to GCA	HIV-1 Specific RTI	L-697,661	Y	Y	4			(22)
V 108 I	GTA to ATA	HIV-1 Specific RTI	Loviride (R89439, α -APA)	Y	?				(48)
V 108 I	GTA to GCA	HIV-1 Specific RTI	MKC-442 (I-EBU)	Y	?				(49)
V 108 I	GTA to ATA	HIV-1 Specific RTI	Nevirapine	N	Y				(29)
V 108 I	GTT to GAT	HIV-1 Specific RTI	TIBO R82913	N	Y	>100	R82150 (>100)		(52)
V 108 I	GTA to ATA	HIV-1 Specific RTI	Trovirdine	Y	?			Found in combination with K101Q	(43,44)
Y 115 F	TAT to TTT	Nucleoside RTI	1592U89	Y	N	2		K65R/L74V and/or Y115F with M184V: 10 fold; L74V/Y115F/M184V: 11-fold	(4,5)
E 138 K	GAG to AAG	HIV-1 Specific RTI	TSAO	Y	?	> 100		E138A (GAG to GCG) in TSAO-naive patients confers TSAO resistance	(53,54,55)
E 138 K	GAG to AAG	HIV-1 Specific RTI	MKC-442 (I-EBU)	Y	N		TSAOs	Obtained in the concomitant presence of low 3TC concentrations	(56)
E 138 K	GAG to AAG	HIV-1 Specific RTI	TIBO R82913	Y	?		TSAOs	Found in combination with L100I	(31)
E 138 K	GAG to AAG	HIV-1 Specific RTI	UC-82	Y	?	5	TSAOs	Activity of UC-82 versus L100I, K103N, V106A, E138K, Y181C and Y188L reduced by 2-, 6-, 1.5-, 2-, 4- and 200-fold, respectively, compared to wild type	(36,37)

Mutations in HIV-1 RT that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
E 138 K	GAG to AAG	HIV-1 Specific RTI	UC-84 (615985)	Y	?	> 100	TSAOs		(34,57)
T 139 I	ACA to ATA	HIV-1 Specific RTI	Calanolide A	Y	?	> 70	Not other NNRTIs		(38)
G 141 E	GGG to GAG	HIV-1 Specific RTI	UC-16	Y	?			K101I/G141E: 10-fold	(34)
S 156 A	TCA to GCA	Pyrophosphate Analogue RTI	Foscarnet (PFA)	Y	N	4.5			(19)
Q 161 L	CAA to CTA	Pyrophosphate Analogue RTI	Foscarnet (PFA)	Y	Y	5		Q161L/H208Y: 9-fold; Q161L/H208Y reverses effects of AZT mutations D67N/K70R/T215Y/K219Q	(18)
V 179 D	GTT to GAT	HIV-1 Specific RTI	DMP 266 (L-743,726)	Y	?			L100I/V179D/Y181C: 1,000-fold	(26,27)
V 179 D	GTT to GAT	HIV-1 Specific RTI	L-697,661	N	Y	4			(22)
V 179 D	GTT to GAT	HIV-1 Specific RTI	TIBO R82913	N	Y	20	R82150 (20)	Untreated patient	(58)
V 179 D	GTT to GAT	HIV-1 Specific RTI	Trovirdine	Y	?			Found in combination with K103R or Y181C; V179D/Y181C: > 1,000-fold	(43,44)
V 179 D	GTT to GAT	HIV-1 Specific RTI	UC-10 (645129)	Y	?	16			(34)
V 179 E	GTT to GAG	HIV-1 Specific RTI	L-697,661	N	Y	8			(22)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	α -APA R18893 (loviride analog)	Y	?				(59)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	BHAP U-87201E (atevirdine)	N	Y			K103N and Y181C observed with monotherapy	(40)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	BHAP U-88204E	Y	?				(25)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	BHAP U-90152 (delavirdine)	?	Y			K103N/Y181C seen with monotherapy and combination therapy	(45)

Mutations in HIV-1 RT that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold- resistance	Cross-resistance (-fold)	Comments	Refs
Y 181 C	TAT to TGT	HIV-1 Specific RTI	BM+51.0836	Y	?				(60)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	DMP 266 (L-743,726)	Y	?	4		L100I/V179D/Y181C: 1,000-fold	(26,27,28)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	E-EBU	Y	?				(50)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	E-EPSeU	Y	?	> 50		Y188C confers greater resistance than Y181C	(61)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	E-EPU	Y	?	> 95		Y188C confers greater resistance than Y181C	(61)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	L-697,593	Y	?	> 100		K103N/Y181C: > 1,000-fold	(46)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	L-697,661	Y	Y	> 30		K103N and Y181C most common with monotherapy	(22,47)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	Loviride (R89439, α -APA)	?	Y				(62)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	Nevirapine	Y	Y	> 100	Other NNRTIs	Can suppress effects of AZT mutations	(23,63,64)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	NSC 648400 (E-BPTU)	Y	?	160	Other NNRTIs		(65)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	TIBO R82913	Y	?	> 100		K103N/Y181C: > 1,000-fold	(33)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	Trovirdine	Y	?		Nevirapine; 9-chloro-TIBO	V179D/Y181C: > 1,000-fold; Found in combination with K103R or V179D	(43,44)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	UC-10 (645129)	Y	?			K101E/Y181C: 200-fold	(35)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	UC-32 (645542)	Y	?	38			(35)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	UC-38 (629243)	Y	?	8-149	Other NNRTIs		(35,66)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	UC-57 (647014)	Y	?			K101E/Y181C: 58-fold	(35)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	UC-68 (638532)	Y	?	5			(35)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	UC-69 (646989)	Y	?			V106A/V181C: 166-fold	(35)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	UC-80 (639475)	Y	?	18			(35)
Y 181 C	TAT to TGT	HIV-1 Specific RTI	UC-81 (615727)	Y	?	53			(34,67)

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Y 181 C	TAT to TGT	HIV-1 Specific RTI	UC-84 (615985)	Y	?	> 118			(35)
Y 181 I	TGT to ATT	HIV-1 Specific RTI	BHAP U-88204E	Y	Y			Appeared after treatment of Y181C-mutated virus with BHAP; high-level resistance to BHAP, nevirapine and TIBO; observed in one nevirapine-treated patient	(68)
Y 181 I	TAT to ATT	HIV-1 Specific RTI	MKC-442 (I-EBU)	Y	N	1,000	All NNRTIs		(56)
Y 181 I	TGT to ATT	HIV-1 Specific RTI	Nevirapine	N	Y	High-level		Observed in one patient	(69)
M 184 I	ATG to ATA	Nucleoside RTI	3TC (lamivudine)	Y	Y			M184V and M184I can suppress effects of AZT resistance mutations	(70,71,72,73)
M 184 T		Nucleoside RTI	3TC (lamivudine)	Y	?			Reduced replication capacity and RT activity	(74)
M 184 V	ATG to GTG	Nucleoside RTI	3TC (lamivudine)	Y	Y	>100	ddI; ddC; (-)-FTC	M184V and M184I can suppress effects of AZT resistance mutations; GTA seen in MT-2 cells in culture	(70,71,72)
M 184 V	ATG to GTG	Nucleoside RTI	ddC	Y	Y	2-5	ddI; 3TC; (-)-FTC		(75)
M 184 V	ATG to GTG	Nucleoside RTI	(-)FTC	Y	?	> 100	3TC	M184V can suppress effects of AZT mutations	(70,71)
M 184 V	ATG to GTG	Nucleoside RTI	1592U89	Y	N	3	3TC; ddI; ddC	K65R/L74V and/or Y115F with M184V: 10 fold; K65R/M184V: 8-fold; L74V/M184V: 9-fold resistance; L74V/Y115F/M184V: 11-fold	(4,5)
M 184 V	ATG to GTG	Nucleoside RTI	ddI	Y	Y	2-5	ddC; 3TC;(-)-FTC	Rarely observed in patients receiving ddI	(75)
M 184 V	ATG to GTG	Nucleoside RTI	L-FddC	Y	?	> 100	3TC; (-)-FTC		(76)
Y 188 C	TAT to TGT	HIV-1 Specific RTI	E-EPSeU	Y	?	> 250		Y188C is the predominant mutation for E-EPSeU; Y188C confers greater resistance than Y181C	

Mutations in HIV-1 RT that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
Y 188 C	TAT to TGT	HIV-1 Specific RTI	E-EPU	Y	?	> 250		Y188C confers greater resistance than Y181C	(61)
Y 188 C	TAT to TGT	HIV-1 Specific RTI	HEPT	Y	?				(50)
Y 188 C	TAT to TGT	HIV-1 Specific RTI	Nevirapine	N	Y				(29)
Y 188 H	TAT to CAT	HIV-1 Specific RTI	BHAP U-87201E (atevirdine)	N	Y			K101E, Y188H, E233Y and K238T observed with U-87201E/AZT combination therapy	(40)
Y 188 H	TAT to CAT	HIV-1 Specific RTI	TIBO R82913	Y	?				(31)
Y 188 H/L	TAT to CAT/ CTT	HIV-1 Specific RTI	Loviride (R89439, α -APA)	?	Y				(62)
Y 188 L	TAT to TTA	HIV-1 Specific RTI	DMP 266 (L-743,726)	Y	?	1,000			(28)
Y 188 L	TAT to TTA	HIV-1 Specific RTI	TIBO R82913	N	Y				(58)
V 189 I	GTA to ATA	HIV-1 Specific RTI	HBY 097	Y	?	2	Other NNRTIs (2-6)		(15)
G 190 A	GGA to GCA	HIV-1 Specific RTI	Loviride (R89439, α)	?	Y				(77)
G 190 A	GGA to GCA	HIV-1 Specific RTI	Nevirapine	N	Y				(23)
G 190 E	GGA to GAA	HIV-1 Specific RTI	AAP-BHAP (U-104489)	Y	?				(78)
G 190 E	GGA to GAA	HIV-1 Specific RTI	HBY 097	Y	?		Other NNRTIs	Reduces enzymatic activity of RT and viral replication competency	(79)
G 190 E	GGA to GAA	HIV-1 Specific RTI	S-2720	Y	?			Mutation decreases RT activity and viral replication competency	(80)
G 190 E	GGA to GAA	HIV-1 Specific RTI	UC-38 (629243)	Y	N			K101E/G190E: > 100-fold; cross resistance to: TSAO-m ³ T, Nevirapine, TIBO R82913, BHAP U88204; susceptible to L697,661	(34,42)
G 190 Q	GGA to CAA	HIV-1 Specific RTI	HBY 097	Y	?		Other NNRTIs	Appears exclusively in connection with V179D change	(15)

Mutations in HIV-1 RT that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
G 190 T	GGA to ?	HIV-1 Specific RTI	HBY 097					Appears under lowered drug concentration selection	(51)
H 208 Y	CAT to TAT	Pyrophosphate Analogue RTI	Foscarnet (PFA)	Y	Y	2		Q161L/H208Y: 9-fold PFA resistance; increased susceptibility to AZT (100-fold), nevirapine (20-fold) and TIBO R82150 (30-fold); Q161L/H208Y reverses effects of AZT mutations D67N, K70R, T215Y and K219Q	(18)
L 210 W	TTG to TGG	Nucleoside RTI	AZT	Y	Y			Mutation arises after prolonged AZT therapy in the context of mutations M41L and T215Y	(81,82)
T 215 F	ACC to TTC	Nucleoside RTI	AZT	?	Y		K67N/K70R/T215Y/K219Q: 120-fold	(1,2,3)	
T 215 Y	ACC to TAC	Nucleoside RTI	AZT	Y	Y		K67N/K70R/T215Y/K219Q: 120-fold Effect of T215Y is reversed by a ddI mutation (L74V), NNRTI mutations (L100I;Y181C) or (-)FTC/3TC mutations (M184I/V); M41L/T215Y: 60-70-fold	(1,2,3)	
Y 215 C	TTC to TGC	Nucleoside RTI	ddC	N	Y	4	Arises on background of T215Y AZT resistance	(83)	
K 219 E	AAA to GAA	Nucleoside RTI	AZT	Y	N				(1,2,3)
K 219 Q	AAA to CAA	Nucleoside RTI	AZT	?	Y		K67N/K70R/T215Y/K219Q: 120-fold	(1,2,3)	
E 233 V	GAA to GTA	HIV-1 Specific RTI	BHAP U-87201E (atevirdine)	N	Y		K101E, Y188H, E233Y and K238T observed with U-87201E/AZT combination therapy	(40)	
P 236 L	CCT to CTT	HIV-1 Specific RTI	BHAP U-87201E (atevirdine)	Y	N				(84)
P 236 L	CCT to CTT	HIV-1 Specific RTI	BHAP U-90152 (delavirdine)	Y	Y		Sensitizes RT 10-fold to nevirapine, TIBO R82913 and L-697,661	(84)	
P 236 L	CCT to CTT	HIV-1 Specific RTI	HEPT	Y	?				(65)
K 238 T	AAA to ACA	HIV-1 Specific RTI	BHAP U-87201E (atevirdine)	N	Y		K101E, Y188H, E233Y and K238T observed with U-87201E/AZT combination therapy	(40)	

Mutations in Protease that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Comments	Refs
R 8 K	CGA to AAA	Protease Inhibitor	A-77003	Y	?	10	R8K/M46I/G48V: 20-fold	(85, 86)
R 8 Q	CGA to CAA	Protease Inhibitor	A-77003	Y	?	10	M46I improves replication competency of R8Q mutant	(85,87)
L 10 F	CTC to TTC	Protease Inhibitor	DMP 450	Y	?		Probably compensatory	(88,89)
L 10 F	CTC to GGC	Protease Inhibitor	VB 11,328	Y	?		L10F/I84V: 8-fold	(90)
L 10 F	CTC to CGC	Protease Inhibitor	VX-478 (141W94)	Y	?			(91)
L 10 F	CTC to CGC	Protease Inhibitor	XM323				L10F/V82A: 2-fold; L10F/K45I/I84V: 50-fold	(92)
L 10 F	CTC to CGC	Protease Inhibitor	SC-55389A	Y	?		L10F/N88S: 10-fold	(93,94)
L 10 I	CTC to ATC	Protease Inhibitor	MK-639 (L-735,524, indinavir)	?	Y			(95)
L 10 I		Protease Inhibitor	Ro 31-8959 (saquinavir)		Y		Found in combination with G48V in vivo	(96)
L 10 R	CTC to CGC	Protease Inhibitor	MK-639 (L-735,524, indinavir)	N	Y		L10R/M46I/L63P/V82T: 4-fold; L10R/M46I/L63P/V82T/I84V: 8-fold	(95)
L 10 V	CTC to GTC	Protease Inhibitor	MK-639 (L-735,524, indinavir)	?	Y			(95)
K 20 M	AAG to ATG	Protease Inhibitor	MK-639 (L-735,524, indinavir)	?	Y			(95)
K 20 R	AAG to AAA	Protease Inhibitor	ABT-538 (ritonavir)	N	Y		K20R/M36I/I54V/V82A: 41-fold	(97,98)
K 20 R	AAG to AAA	Protease Inhibitor	MK-639 (L-735,524, indinavir)	?	Y			(95)

Mutations in Protease that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance	Cross-resistance (-fold)	Comments	Refs
L 23 I	CTA to ATA	Protease Inhibitor	BILA 2185 BS	Y	?			p1/p6 cleavage site mutation (L to F (CTT to TTT) at P1'); p7(NC)/p1 cleavage site mutation (Q to R (CAG to CGG) at P3, A to V (GCT to GTT) at P2'); L23I/V32I/M46I/I47V/I54M/A71V/I84V:1300-fold	(99)
L 24 I	TTA to ATA	Protease Inhibitor	MK-639 (L-735,524, indinavir)	?	Y				(95)
L 24 V	TTA to GTA	Protease Inhibitor	SC-52151	Y	?	10-20		L24V/G48V/A71V/V75I/P81T: 1000-fold	(94)
D 30 N	GAT to AAT	Protease Inhibitor	AG1343 (nelfinavir)	Y	Y			D30N/A71V: 7-fold; D30N and N88D are most common in vivo after 24 weeks of therapy; they do not cause cross-resistance to other protease inhibitors	(100,101)
V 32 I	GTA to ATA	Protease Inhibitor	A-75925	Y	?	40		V32I and V82I are synergistic mutations yielding 20-fold enzyme resistance	(87,102)
V 32 I	GTA to ATA	Protease Inhibitor	A-77003	Y	?	7 (enzyme resist.)		V32I appears first; progression to V32I/ M46V and V32I/M46V/A71V/V82A occurs even in the absence of drug	(87,103)
V 32 I	GTA to ATA	Protease Inhibitor	BILA 1906 BS	Y	?			V32I/A71V: 3-fold; V32I/A71V/M46I/ I84V: 500-1,000-fold	(99,104,105)
V 32 I	GTA to ATA	Protease Inhibitor	BILA 2011 (palinavir)	Y	?	1200		Other mutations found in p1/p6 cleavage site	(105)
V 32 I	GTA to ATA	Protease Inhibitor	KNI-272	Y	?	2		V32I/M46I/I84V: 37-fold; V32I/L33F/ K45I/F53L/A71V/I84V/L89M: 130-fold	(106)
V 32 I	GTA to ATA	Protease Inhibitor	MK-639 (L-735, 524, indinavir)	Y	Y			V32I/M46L/V82A: 3-fold; V32I/M46L/ A71V/V82A: 14-fold	(86)

Mutations in Protease that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
L 33 F	TTA to TTC	Protease Inhibitor	ABT-538 (ritonavir)	N	Y				(97)
M 36 I	ATG to ATA	Protease Inhibitor	ABT-538 (ritonavir)	N	Y			M36I/I54V/A71T/V82T: 8-fold; K20R/M36I/I59V/V82A: 41-fold; In vivo, V82 occurs first, often followed by changes at I54, A71 and M36	(97,98)
M 36 I		Protease Inhibitor	AG1343 (nelfinavir)		Y			M46I/L63P/A71V/I84V: 30-fold	(100,101)
K 45 I	AAA to ATA	Protease Inhibitor	XM323					L10F/K45I/I84V: 50-fold	(86)
M 46 F	ATG to TTC	Protease Inhibitor	A-77003	Y	?	4 (enzyme resist.)		Seen with V82A	(87)
M 46 I	ATG to ATA	Protease Inhibitor	A-77003	Y	?			No effect on susceptibility but improves replication competency of R8Q mutant; R8K/M46I/G48V: 20-fold	(85,86)
M 46 I	ATG to ATA	Protease Inhibitor	ABT-538 (ritonavir)	Y	Y			M46I/L63P/A71V/V82F/I84V: 27-fold	(97,98)
M 46 I	ATG to ATA	Protease Inhibitor	AG1343 (nelfinavir)	Y	Y				
M 46 I	ATG to ATA	Protease Inhibitor	BILA 1906 BS	Y	?			V32I/A71V/M46I/I84V: 500-1,000-fold	(96,104,105)
M 46 I	ATG to ATA	Protease Inhibitor	DMP 450	Y	?			Probably compensatory	(88,89)
M 46 I	ATG to ATA	Protease Inhibitor	MK-639 (L-735,524, indinavir)	N	Y			M46I/L63P/V82T: 4-fold; L10R/M46I/L63P/V82T: 4-fold; L10R/M46I/L63P/V82T/I84V: 8-fold	(95,107)
M 46 I	ATG to ATA	Protease Inhibitor	VB 11,328	Y	?			I50V/M46I/I47V: 20-fold	(86,90)
M 46 I	ATG to ATA	Protease Inhibitor	VX-478 (141W94)	Y	?	Nil			
M 46 L	ATG to TTC	Protease Inhibitor	A-77003	Y	?	2-3 (enzyme resist.)			(87)
M 46 L	ATG to TTG	Protease Inhibitor	BILA 1906 BS	Y	?			p1/p6 cleavage site mutation (L to F (CTT to TTT) at P1'); p7(NC)/p1 cleavage site mutation (Q to R (CAG to CGG) at P3, A to V (GCT to GTT) at P2')	(99,104,105)

Mutations in Protease that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
M 46 L	ATG to TTG	Protease Inhibitor	MK-639 (L-735,524, indinavir)	Y	Y			V32I/M46L/A71V/V82A: 14-fold; V32I/M46L/V82A: 3-fold	(86)
M 46 L	ATG to CTG	Protease Inhibitor	XM323	Y	?			M46L/V82A: 7-fold; M46L/V82A/L97V: 11-fold	(92)
M 46 V		Protease Inhibitor	A-77003	Y	?			V32I appears first; progression to V32I/M46V and V32I/M46V/A71V/V82A occurs even in the absence of drug	(87,103)
I 47 V	ATA to CTA	Protease Inhibitor	VB 11,328	Y	?			I50V/M46I/I47V: 20-fold	(86,90)
I 47 V	ATA to CTA	Protease Inhibitor	VX-478 (141W94)	Y	?	Nil			(108)
G 48 V	GGG to GTG	Protease Inhibitor	A-77003	Y	?			R8K/M46I/G48V: 20-fold; G48V/I82T: 100-fold	(86)
G 48 V	GGG to GTG	Protease Inhibitor	Ro 31-8959 (saquinavir)	Y	Y			Found in comb. with L10I in vivo; G48V/I84V/L90M: 30-fold; G48V/L90M: >100-fold enzyme resistance; G48V/L90M/I54V: > 50-fold (subtype B or O); No back mutation seen in absence of drug at passage 26	(109,110)
G 48 V	GGG to GTG	Protease Inhibitor	SC-52151	Y	?			G48V/V82A, G48V/L63P/V82A or I54T: 10- to 20-fold; L24V/G48V/A71V/V75I/P81T: 1000-fold	(93,94)
I 50 V	ATT to GTT	Protease Inhibitor	VB 11,328	Y	?	3		I50V/M46I/I47V: 20-fold	(86)
I 50 V	ATT to GTT	Protease Inhibitor	VX-478 (141W94)	Y	?	3			(108)
I 54 L	ATC to ?	Protease Inhibitor	ABT-538 (ritonavir)	N	Y			In vivo, V82 occurs first, often followed by changes at I54, A71 and M36	(97,98)

Mutations in Protease that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
I 54 V	ATC to GTC	Protease Inhibitor	ABT-538 (ritonavir)	N	Y			I54V/V82T: 9-fold; K20R/M36I/I54V/ V82A: 41-fold; M36I/I54V/A71V/ V82T: 8-fold; I54V/A71V/L90M: 7- fold; In vivo, V82 occurs first, often followed by changes at I54, A71 and M36	
I 54 V	ATC to GTC	Protease Inhibitor	MK-639 (L- 735,524, indinavir)	?	Y				(95)
I 54 V	ATA to GTA	Protease Inhibitor	Ro 31-8959 (saquinavir)	Y				In subtype O	(109,110)
I 54 V	ATC to GTC	Protease Inhibitor	Ro 31-8959 (saquinavir)	Y				In subtype B	(109,110)
D 60 E	GAT to GAA	Protease Inhibitor	DMP 450	Y	?			Probably compensatory	(81,88)
L 63 P	CTC to CCC	Protease Inhibitor	AG1343 (nelfinavir)		Y			M46I/L63P/A71V/I84V: 30-fold	(100,101)
L 63 P	CTC to CCC	Protease Inhibitor	BILA 2011 (palinavir)	Y	?				
L 63 P	CTC to CCC	Protease Inhibitor	MK-639 (L- 735,524, indinavir)	N	Y			M46I/L63P/V82T: 4-fold; L10R/M46I/ L63P/V82T/I84V: 8-fold; L10R/M46I/ L63P/V82T: 4-fold	(95,107)
A 71 T	GCT to ACT	Protease Inhibitor	BMS 186,318	Y	?			A71T/V82A: 15-fold	(111,112)
A 71 T	GCT to ACT	Protease Inhibitor	MK-639 (L- 735,524, indinavir)	?	Y				(95)
A 71 V		Protease Inhibitor	A-77003	Y	?			V32I appears first; progression to V32I/ M46V and V32I/M46V/A71V/V82A occurs even in the absence of drug; M46I/L63P/A71V/V82F/I84V: 27-fold	(87,103)

Mutations in Protease that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
A 71 V	GCT to GTT	Protease Inhibitor	ABT-538 (ritonavir)	Y	Y		K20R/M36I/I54V/A71V/V82T: 28-fold; M36I/I54V/A71V/V82T: 8-fold; I54V/A71V/I/V82A/L90M: 7-fold; In vivo, V82 occurs first, often followed by changes at I54, A71 and M36		
A 71 V	GCT to GTT	Protease Inhibitor	AG1343 (nelfinavir)	Y	?	5	D30N/A71V: 7-fold; M46I/L63P/A71V/I84V: 30-fold	(100,101)	
A 71 V	GCT to GTT	Protease Inhibitor	BILA 1906 BS	Y	?		V32I/A71V: 3-fold; V32I/A71V/M46I/I84V: 500-1,000-fold	(99,104,105)	
A 71 V	GCT to GTT	Protease Inhibitor	BILA 2011 (palinavir)	Y	?				
A 71 V	GCT to GTT	Protease Inhibitor	MK-639 (L-735,524, indinavir)	Y	Y		V32I/M46L/A71V/V82A: 14-fold	(86)	
A 71 V	GCT to GTT	Protease Inhibitor	SC-52151	Y	?		A71V/V75I/P81T: 20- to 30-fold; L24V/G48V/A71V/V75I/P81T: 1000-fold; N88D or I11V/M46I/F53L/A71V/N88D: 10- to 20-fold	(93,94)	
V 75 I	GTA to ATA	Protease Inhibitor	SC-52151	Y	?		L24V/G48V/A71V/V75I/P81T: 1000-fold; A71V/V75I/P81T: 20- to 30-fold; L24V/G48V/A71V/V75I/P81T: 1000-fold	(93,94)	
V 77 I		Protease Inhibitor	AG1343 (nelfinavir)	Y	Y				
P 81 T	CCT to ACT	Protease Inhibitor	SC-52151	Y	?		A71V/V75I/P81T: 20- to 30-fold; L24V/G48V/A71V/V75I/P81T: 1000-fold	(93,94)	
I 82 T	ATC to ACC	Protease Inhibitor	A-77003	Y	?		G48V/I82T: 100-fold (82T was derived from in vitro passage of 82I)	(111)	

Mutations in Protease that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
V 82 A	GTC to GCC	Protease Inhibitor	A-77003	Y	?			Rare; seen with M46F; V32I appears first; progression to V32I/M46V and V32I/M46V/A71V/V82A occurs even in the absence of drug	(87,103,111)
V 82 A	GTC to GCC	Protease Inhibitor	ABT-538 (ritonavir)	N	Y	2		In vivo, V82 occurs first, often followed by changes at I54, A71 and M36	(97,98)
V 82 A	GTC to GCC	Protease Inhibitor	BMS 186,318	Y	?			A71T/V82A: 15-fold	(112,113)
V 82 A	GTC to GCC	Protease Inhibitor	MK-639 (L-735,524, indinavir)	Y	Y			V32I/M46L/V82A: 3-fold; V32I/M46L/A71V/V82A: 14-fold	(86,95,107,114)
V 82 A	GTC to GCC	Protease Inhibitor	P9941	Y	?	6-8			(115)
V 82 A	GTC to GCC	Protease Inhibitor	SC-52151	Y	?			G48V/V82A, G48V/L63P/V82A or I54T: 10- to 20-fold	(93,94)
V 82 A		Protease Inhibitor	SKF108922	Y	?				
V 82 A	GTC to GCC	Protease Inhibitor	XM323	Y	?			V82A/M46L: 7-fold; V82A/M46L/L97V: 11-fold; L10F/V82A: 2-fold; V82A/L97V: 3-fold	(92)
V 82 F	GTC to TTC	Protease Inhibitor	ABT-538 (ritonavir)	Y	Y			V82F/I84V: 8- to 10-fold; M46I/L63P/A71V/V82F/I84V: 27-fold	(97,98)
V 82 F	GTC to TTC	Protease Inhibitor	MK-639 (L-735,524, indinavir)	?	Y				(95,107)
V 82 F	GTC to TTC	Protease Inhibitor	XM323	Y	?			V82F/I84V: 92-fold	(92)
V 82 I	GTC to ATC	Protease Inhibitor	A-77003	Y	?			No resistance alone but V32I and V82I are synergistic mutations yielding 20-fold enzyme resistance (82T was derived from in vitro passage of 82I)	(87,111)
V 82 I	GTC to ATC	Protease Inhibitor	XM323	Y	?	<2			(92)
V 82 S	GTC to TCC	Protease Inhibitor	ABT-538 (ritonavir)	N	Y	6		In vivo, V82 occurs first, often followed by changes at I54, A71 and M36	(97,98)

Mutations in Protease that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
V 82 T	GTC to ACC	Protease Inhibitor	ABT-538 (ritonavir)	N	Y	3		In vivo, V82 occurs first, often followed by changes at I54, A71 and M36; V82T has reduced replication efficacy in natural background; M36I/I54V/A71V/V82T: 8-fold; I54V/V82T: 9-fold	
V 82 T	GTC to ACC	Protease Inhibitor	MK-639 (L-735,524, indinavir)	N	Y			M46I/L63P/V82T: 4-fold; L10R/M46I/L63P/V82T: 4-fold; L10R/M46I/L63P/V82T/I84V: 8-fold	(95,107)
V 82 T		Protease Inhibitor	SKF108842	Y	?				(116)
I 84 A	ATA to GCA	Protease Inhibitor	BILA 1906 BS	Y	?				(99,104,105)
I 84 A	ATG to ATA	Protease Inhibitor	BILA 2011 (palinavir)	Y	?			I84A is the most common mutation	(99,104,105)
I 84 V	ATA to GTA	Protease Inhibitor	ABT-538 (ritonavir)	Y	Y			M46I/L63P/A71V/V82F/I84V: 27-fold; V82F/I84V: 8- to 10-fold; M46I/L63P/A71V/V82F/I84V: 27-fold	(97,98)
I 84 V	ATA to GTA	Protease Inhibitor	AG1343 (nelfinavir)		?			M46I/L63P/A71V/I84V: 30-fold	(100,101)
I 84 V	ATA to GTA	Protease Inhibitor	BILA 1906 BS	Y	?			V32I/A71V/M46I/I84V: 500-1,000-fold	(99,104,105)
I 84 V	ATA to GTA	Protease Inhibitor	DMP 450	Y	?			S1 subsite	(88,89)
I 84 V	ATA to CTA	Protease Inhibitor	MK-639 (L-735,524, indinavir)	N	Y			G48V/I84V/L90M: 30-fold; L10R/M46I/L63P/V82T/I84V: 8-fold	(95,107)
I 84 V	ATA to GTA	Protease Inhibitor	Ro 31-8959 (saquinavir)	Y	?				(86)
I 84 V	ATA to GTA	Protease Inhibitor	RPI-312	Y	?	5			(117)
I 84 V		Protease Inhibitor	SKF108842	Y	?				(116)
I 84 V	ATA to GTA	Protease Inhibitor	VB 11,328	Y	?			L10F/I84V: 8-fold	(86,90)
I 84 V	ATA to GTA	Protease Inhibitor	VX-478 (141W94)	Y	?				(108)

Mutations in Protease that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
I 84 V	ATA to GTA	Protease Inhibitor	XM323	Y	?	12		V82F/I84V: 92-fold; L10F/K45I/I84V: 50-fold	(86,92)
N 88 D		Protease Inhibitor	AG1343 (nelfinavir)	Y	Y			D30N and N88D are most common in vivo after 24 weeks of therapy; they do not cause cross-resistance to other protease inhibitors	(100,101)
N 88 D	AAT to GAT	Protease Inhibitor	SC-52151	Y	?			N88D or I11V/M46I/F53L/A71V/ N88D: 10- to 20-fold	(93,94)
N 88 S	AAT to AGT	Protease Inhibitor	SC-55389A	Y	?	20		N88S/L10F: 10-fold	(93,94)
L 90 M	TTG to ATG	Protease Inhibitor	ABT-538 (ritonavir)	N	Y			82A/54V/I/71V/90L/M: 7-fold	(97,98)
L 90 M	TTG to ATG	Protease Inhibitor	AG1343 (nelfinavir)	N	Y			Rare in patients	(100,101)
L 90 M	TTG to ATG	Protease Inhibitor	MK-639 (L-735,524, indinavir)	?	Y				(95,107)
L 90 M	TTG to ATG	Protease Inhibitor	Ro 31-8959 (saquinavir)	Y	Y			G48V/L90M: >100-fold enzyme resistance; double mutant rare in vivo; L90M most common in vivo; G48V/I84V/L90M: 30-fold	(109)
L 97 V	TTA to GTA	Protease Inhibitor	XM323	Y	?			No resistance alone; V82A/L97V: 3-fold; V82A/M46L/L97V: 11-fold	(92)

Mutations in Envelope that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
S 113 N	AGT to AAT	Fusion/Binding Inhibitor	Dextran sulphate (DS)	Y	?			S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold; 113 is in the V1 loop region	(118,119)
S 134 N	AGC to AAC	Fusion/Binding Inhibitor	Dextran sulphate (DS)	Y	?			V2 loop region; S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold	(118,119)
F 145 L	TTC to TTA	Fusion/Binding Inhibitor	JM-3100	Y	?			Combination of mutations: 2- to 100-fold	(120,121)
N 188 K	AAT to AAA	Fusion/Binding Inhibitor	Siamycin I	Y	?			N188K/G332E/N351D/A550T/N633D/L762S: 9-fold	(122)
I 228 V	ATA to GTA	Fusion/Binding Inhibitor	JM-2763	Y	?			Combination of mutations	
K 269 E	AAA to GAA	Fusion/Binding Inhibitor	Dextran sulphate (DS)	Y	?			V3 loop region; S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold	(118,119)
N 270 S	AAT to AGT	Fusion/Binding Inhibitor	JM-3100	Y	?				
R 272 T	AGA to ACA	Fusion/Binding Inhibitor	JM-3100	Y	?				
S 274 R	AGT to AGA	Fusion/Binding Inhibitor	JM-2763	Y	?			Combination of mutations: 95- to 792-fold	(120,121)
S 274 R	AGT to AGA	Fusion/Binding Inhibitor	JM-3100	Y	?	DS (> 7 to 6,667)			
Q 278 H	CAG to CAT	Fusion/Binding Inhibitor	Dextran sulphate (DS)	Y	?			V3 loop region; S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold	(118,119)
Q 278 H	CAG to CAT	Fusion/Binding Inhibitor	JM-2763	Y	?				
Q 278 H	CAG to CAC	Fusion/Binding Inhibitor	JM-3100	Y	?				
I 288 V	ATA to GTA	Fusion/Binding Inhibitor	JM-3100	Y	?				
N 293 D	AAT to GAT	Fusion/Binding Inhibitor	Dextran sulphate (DS)	Y	?			V3 loop region; S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold	(118,119)
N 293 H	AAT to CAT	Fusion/Binding Inhibitor	JM-3100	Y	?				
A 297 T	GCA to ACA	Fusion/Binding Inhibitor	JM-2763	Y	?				
A 297 T	GCA to ACA	Fusion/Binding Inhibitor	JM-3100	Y	?				
N 323 S	AAT to AGT	Fusion/Binding Inhibitor	Dextran sulphate (DS)	Y	?			C3 region; S113N/S134N/K269E/Q278E/N293D/N323S/R387I: 250-fold	(118,119)

Mutations in Envelope that confer drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	Fold-resistance (-fold)	Cross-resistance	Comments	Refs
G 332 E	GGA to GAA	Fusion/Binding Inhibitor	Siamycin I	Y	?			N188K/G332E/N351D/A550T/N633D/ L762S: 9-fold	(122)
N 351 D	AAT to GAT	Fusion/Binding Inhibitor	Siamycin I	Y	?			N188K/G332E/N351D/A550T/N633D/ L762S: 9-fold	(122)
P 385 L	CCA to CTA	Fusion/Binding Inhibitor	JM-2763	Y	?				
P 385 L	CCA to CTA	Fusion/Binding Inhibitor	JM-3100	Y	?				
R 387 I	AGA to ACA	Fusion/Binding Inhibitor	Dextran sulphate (DS)	Y	?			CD4 binding region; S113N/S134N/ K269E/Q278E/N293D/N323S/R387I: 250-fold	(118,119)
Q 410 E	CAA to GAA	Fusion/Binding Inhibitor	JM-3100	Y	?				
S 433 P	TCC to CCC	Fusion/Binding Inhibitor	JM-3100	Y	?				
V 457 I	GTA to ATA	Fusion/Binding Inhibitor	JM-3100	Y	?				
A 550 T	GCC to ACC	Fusion/Binding Inhibitor	Siamycin I	Y	?			N188K/G332E/N351D/A550T/N633D/ L762S: 9-fold	(122)
N 633 D	AAT to GAT	Fusion/Binding Inhibitor	Siamycin I	Y	?			N188K/G332E/N351D/A550T/N633D/ L762S: 9-fold	(122)
L 762 S	TTG to TCG	Fusion/Binding Inhibitor	Siamycin I	Y	?			N188K/G332E/N351D/A550T/N633D/ L762S: 9-fold	(122)

Mutations that confer multiple drug resistance, ordered by position.

Amino Acid Change	Codon Change	Class of Drug	Compound	In vitro	In vivo	-Fold -resistance	Cross-resistance (-fold)	Comments	Refs
A 62 V	GCC to GTC	Multiple Drug Resistance	AZT+ ddI/ddC	N	Y	Nil		Associated with 75, 77, 116 & 151; A62V/V75I/F77L/F116Y/Q151M: AZT 190-fold	(123,124)
V 75 I	GTA to ATA	Multiple Drug Resistance	AZT+ ddI/ddC	N	Y	Nil		Associated with 77, 116 & 151; A62V/V75I/F77L/F116Y/Q151M: AZT 190-fold	(123,124)
F 77 L	TTC to CTC	Multiple Drug Resistance	AZT+ ddI/ddC	N	Y	Nil		Associated with 75, 116 & 151; A62V/V75I/F77L/F116Y/Q151M: AZT 190-fold	(123,124)
F 116 Y	TTT to TAT	Multiple Drug Resistance	AZT+ ddI/ddC	N	Y	Nil		Associated with 75, 77 & 151; A62V/V75I/F77L/F116Y/Q151M: AZT 190-fold	(123,124)
Q 151 M	CAG to ATG	Multiple Drug Resistance	AZT+ ddI/ddC	N	Y	AZT: 10; ddI: 5		Pivotal MDR mutation (first to occur and is then found in association with various of the other four mutations); A62V/V75I/F77L/F116Y/Q151M: AZT 190-fold; ddI 50-fold; ddC 20-fold; d4T > 10-fold	(123,124,125)

Abbreviations

Amino acids

A	alanine
C	cysteine
D	aspartate
E	glutamate
F	phenylalanine
G	glycine
H	histidine
I	isoleucine
K	lysine
L	leucine
M	methionine
N	asparagine
P	proline
Q	glutamine
R	arginine
S	serine
T	threonine
V	valine
W	tryptophan
Y	tyrosine

Compounds

1592U89	(1 <i>S</i> ,4 <i>R</i>)-4-[2-amino-6-cyclopropyl-amino]-9 <i>H</i> -purin-9-yl]-2-cyclopentene-1-methanol succinate (a carbovir analogue, Glaxo Wellcome)
3TC	(-)- β -L-2',3'-dideoxy-3'-thiacytidine (Glaxo Wellcome)
α -APA R18893	α -nitro-anilino-phenylacetamide
A-77003, A-75925 and A-80987	C2 symmetry-based protease inhibitors (Abbott Laboratories)
AAP-BHAP	bisheteroarylpiperazine analogue (Pharmacia & Upjohn)
ABT-538	C2 symmetry-based protease inhibitor (Abbott Laboratories)
AZdU	3'-azido-2',3'-dideoxyuridine
AZT	3'-azido-3'-deoxythymidine (Glaxo Wellcome)
AZT-p-ddI	3'-azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxyinosinic acid (Ivax)
BHAP	bisheteroarylpiperazine
BILA 1906	<i>N</i> -{1 <i>S</i> -[[[3-[2 <i>S</i> -(1,1-dimethylethyl)amino]carbonyl-4 <i>R</i> -]3-pyridinylmethyl]thio]-1-piperidinyl}-2R-hydroxy-1 <i>S</i> -(phenylmethyl)propyl]amino]carbonyl]-2-methylpropyl}-2-quinolinecarboxamide (Bio-Mega/Boehringer Ingelheim)
BILA 2185	<i>N</i> -(1,1-dimethylethyl)-1-[2 <i>S</i> -[[2-2,6-dimethoxyphenoxy)-1-oxoethyl]amino]-2R-hydroxy-4-phenylbutyl]4 <i>R</i> -pyridinylthio)-2-piperidine-carboxamide (Bio-Mega/Boehringer Ingelheim)
BM+51.0836	thiazolo-isindolinone derivative
BMS 186,318	aminodiol derivative HIV-1 protease inhibitor (Bristol-Myers Squibb)

Abbreviations

Abbreviations (cont)

Compounds (cont)

d4API	9-[2,5-dihydro-5-(phosphonomethoxy)-2-furanyl]adenine (Gilead Sciences)
d4C	2',3'-didehydro-2',3'-dideoxycytidine
d4T	2',3'-didehydro-3'-deoxythymidine (Bristol-Myers Squibb)
ddC	2',3'-dideoxycytidine (Roche)
ddI	2',3'-dideoxyinosine (Bristol-Myers Squibb)
DMP 266	a 1,4-dihydro-2H-3,1-benzoxazin-2-one
DMP 450	[4 <i>R</i> -(4- α ,5- α ,6- β ,7- β)]-hexahydro-5,6-bis(hydroxy)-1,3-bis(3-amino)phenyl)methyl)-4,7-bis(phenylmethyl)-2 <i>H</i> -1,3-diazepin-2-one-bismesylate (Avid Therapeutics)
DXG	(-)- β -D-dioxolane-guanosine
EBU-dM	5-ethyl-1-ethoxymethyl-6-(3,5-dimethylbenzyl)uracil
E-EBU	5-ethyl-1-ethoxymethyl-6-benzyluracil
DS	dextran sulphate
E-EPSeU	1-(ethoxymethyl)-(6-phenylselenyl)-5-ethyluracil
E-EPU	1-(ethoxymethyl)-(6-phenyl-thio)-5-ethyluracil
(-)-FTC	(-)- β -L-2',3'-dideoxy-5-fluoro-3'-thiacytidine (Triangle Pharmaceuticals)
HBY 097	(<i>S</i>)-4-isopropoxycarbonyl-6-methoxy-3-(methylthio-methyl)-3,4-dihydroquinoxalin-2(1 <i>H</i>)-thione
HEPT	1-[(2-hydroxyethoxy)methyl]6-(phenylthio)thymine
JM2763	1,1'-(1,3-propanediyl)-bis-1,4,8,11-tetraazacyclo-tetradecane (Johnson Matthey)
JM3100	1,1'-[1,4-phenylenebis-(methylene)]bis-(1,4,8,11-tetraazacyclotetradecane) octahydrochloride dihydrate (Johnson Matthey)
KNI-272	(2 <i>S</i> ,3 <i>S</i>)-3-amino-2-hydroxy-4-phenylbutyric acid-containing tripeptide
L-697,593	5-ethyl-6-methyl-3-(2-phthalimido-ethyl)pyridin-2(1 <i>H</i>)-one
L-697,661	3-[-(4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino-5-ethyl-6-methylpyridin-2(1 <i>H</i>)-one
L-FDDC	(-)- β -L-5-fluoro-2',3'-dideoxy-cytidine
L-FDOC	(-)- β -L-5-fluoro-dioxolane cytosine
MK-639	hydroxy-aminopentane amide HIV-1 protease inhibitor (Merck & Co)
MKC442	6-benzyl-1-ethoxymethyl-5-isopropyluracil (I-EBU, Triangle Pharmaceuticals/Mitsubishi)
nevirapine	11-cyclopropyl-5,11-dihydro-4-methyl-6 <i>H</i> -dipyridol[3,2-b:2',3'-e]diazepin-6-one (Boehringer Ingelheim)
NNRTI	non-nucleoside reverse transcriptase inhibitor
NSC648400	1-benzyloxymethyl-5-ethyl-6-(alpha-pyridylthio)uracil (E-BPTU)
P9941	[2-pyridylacetyl-IlePheAla-y(CHOH)] ₂ (Dupont Merck)
PFA	phosphonoformate (foscarnet, Astra)
PMEA	9-(2 phosphonylmethoxyethyl)adenine (Gilead Sciences)
PMPA	(<i>R</i>)-9-(2-phosphonyl-methoxypropyl)adenine (Gilead Sciences)
Ro 31-8959	hydroxyethylamine derivative HIV-1 protease inhibitor (Roche)

Abbreviations (cont)**Compounds (cont)**

RPI-312	1-[<i>(3S</i>)-3-(n-alpha-benzyloxycarbonyl)-l-aspariginyl]-amino-2-hydroxy-4-phenyl-butryryl]- <i>n</i> -tert-butyl-l-proline amide (peptidyl protease inhibitor)
RT	reverse transcriptase
S-2720	6-chloro-3,3-dimethyl-4-(isopropenyl-oxycarbonyl)-3,4-dihydro-quinoxalin-2(<i>1H</i>)thione
SC-52151	hydroxyethylurea isostere protease inhibitor (Searle)
SC-55389A	hydroxyethyl-urea isostere protease inhibitor (Searle)
TIBO R82150	(+)-(5 <i>S</i>)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)-imidazo[4,5,1- <i>jk</i>][1,4]-benzodiazepin-2(<i>1H</i>)-thione (Janssen)
TIBO 82913	(+)-(5 <i>S</i>)-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)-imidazo-[4,5,1- <i>jk</i>]-[1,4]benzo-diazepin-2(1 <i>it H</i>)-thione (Janssen)
TSAO-m ³ T	[2',5'-bis- <i>O</i> -(tert-butyl-dimethylsilyl)-3'-spiro-5'-(4'-amino-1',2'-oxathiole-2',2'-dioxide)]- β -D-pentofuranosyl-N ³ -methylthymine
U-90152	1-[3-[(1-methylethyl)-amino]-2-pyridinyl]-4-[[5-[(methylsulphonyl)-amino]-l <i>H</i> -indol-2yl]carbonyl]-piperazine
UC	thiocarboxanilide derivatives (Uniroyal Chemical Co)
UC-781	<i>N</i> -[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furan-carbothioamide
UC-82	<i>N</i> -[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-thiophene-carbothioamide
VB 11,328	hydroxyethyl-sulphonamide protease inhibitor (Vertex Pharmaceuticals)
VX-478	hydroxyethylsulphonamide protease inhibitor (Vertex Pharmaceuticals)
XM 323	cyclic urea protease inhibitor (Dupont Merck)

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